Request for Telephone Interview

Applicant respectfully requests a telephone interview with the Examiner and the Examiner's Supervisor if, upon consideration of this Reply, the Examiner does not deem the application to be in condition for allowance.

Traversal of Restriction Requirement

Applicant respectfully traverses the Examiner's finding that Claims 58-106 are directed to an invention which is "independent or distinct" from the invention originally claimed. Applicant believes that the invention of at least some of claims 58-106 is not independent and distinct from the invention elected for prosecution. However, the Examiner's *de minimus* statement regarding the newly added claims does not provide Applicant with sufficient information to present a comprehensive traversal of the Examiner's holding. For example, the Examiner has failed to indicate exactly how the claims are to be restricted. This is contrary to the instructions provided by the MPEP:

> This is the best way to most clearly and precisely indicate to applicant how the application should be restricted. It consists in identifying each separate subject amongst which restriction is required, and grouping each claim with its subject.
>
> The separate inventions should be identified by a grouping of the claims with a short description of the total extent of the invention claimed in each group, specifying the type or relationship of each group as by stating the group is drawn to a process, or to a subcombination, or to a product, etc., and should indicate the classification or separate status of each group, as for example, by class and subclass. (MPEP §814)

Applicant respectfully submits that the Examiner has not properly set forth the grouping of each of the claims deemed to be drawn to a non-elected invention. It is important for the Examiner to do so in order for Applicant to be fully apprised of the effect of 35 U.S.C. §121 with regard to the various claims of the application. Applicant believes that it would be proper for the Examiner to reconsider and withdraw the holding that Claims 58-106 are directed to an invention which is independent or distinct from the invention elected for prosecution. However, at a minimum Applicant respectfully requests that the Examiner clearly set forth the basis for the restriction of these claims and the groups to which the Examiner deems them to belong.

Rejection of Claims 1, 5, 6, 8 and 45-57 Under 35 U.S.C. §102(e)

Claims 1, 5, 6, 8 and 45-57 are rejected under 35 U.S.C. §102(e) as being anticipated by Lind *et al.* (U.S. Patent No. 6,084,075; Reference A and AC). The Examiner states that Lind *et al.* clearly discloses that the antibody directed to the amino-terminal region of CCR2 designated mAb MCPR-02 is an agonist as shown in Claim 1 of Lind *et al.* The Examiner further states that an agonist by definition is an agent that occupies a cell receptor, and that Applicant's interpretation of the Table III with respect to MCPR-02 is misplaced. The Examiner further states that:

> The said Table clearly shows that the MCPR-02 is exhibiting agonistic characteristics, hence, there should be no doubts that the said antibody is capable of inhibiting chemokine to CCR2 receptor (Office Action, Page 3).

Applicant respectfully submits that the Examiner's assessment of the plain language of the claims of the subject application and his conclusion regarding the impact of the teachings of Lind et al. on the novelty of these claims are incorrect.

Claims 46-51 have been cancelled. Claims 1, 45 and 52 recite the phrase "wherein said antibody or antigen-binding fragment thereof inhibits binding of a chemokine to said receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor."

Lind *et al.* discloses a number of antibodies which bind to CCR2. Some of the antibodies disclosed by Lind *et al.* (antibodies MCPR-03, MCPR-04, MCPR-05 and MCPR-06) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the third extracellular loop (amino acids 273-292) of CCR2. In Table III (col. 14), Lind *et al.* states that these antibodies recognize amino acids 273-292 of CCR2. These antibodies plainly do not anticipate Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof binds the amino-terminal domain of CCR2, as these antibodies of Lind *et al.* do not bind the amino terminal domain of CCR2.

The MCPR-01 and MCPR-02 antibodies disclosed by Lind *et al.* were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the amino-terminal domain (amino acids 24-38) of CCR2. In Table III (col. 14), Lind *et al.* states that these antibodies

recognize amino acids 24-38 of CCR2. However, Table III also provides a summary of the activities of MCPR-01 and MCPR-02. MCPR-01 is disclosed as being neither an agonist nor an antagonist of MCP-1-induced calcium influx or transmigration (Table III), i.e., MCPR-01 neither induced nor inhibited calcium flux and transmigration. Thus, the MCPR-01 antibody does not anticipate Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof inhibits one or more functions associated with binding of the chemokine to said receptor, as MCPR-01 is not disclosed as inhibiting any functions associated with binding of chemokine to CCR2 (e.g., calcium flux or transmigration).

MCPR-02, the antibody particularly noted by the Examiner, is disclosed as being an agonist of MCP-1-induced calcium influx and transmigration (Table III). That is, MCPR-02 is disclosed as stimulating both chemotaxis and calcium influx (col. 12, lines 32-40, and Figure 4B), which are functions associated with binding of chemokine to CCR2. By the Examiner's own statement in the Office Action, "[t]his antibody is an agonist as shown in claim 1 of the ,075 patent ". However, the Examiner also states that an agonist "...by definition is an agent that occupies a cell receptor." Applicant submits that this is not an accurate definition of an "agonist". An "agonist" is more typically defined as an agent which stimulates, promotes, enhances or effects a particular response or signal, and is contrasted with an "antagonist" which reduces, inhibits or interferes with a particular response or signal. However, regardless of the nomenclature which is used to classify the MCPR-02 antibody, the results of Lind *et al.* make clear that MCPR-02 stimulates a rapid and transient rise in Ca2+ concentration in Mono-Mac-1 cells, and allows chemotaxis of Mono-Mac-1 cells (col. 12, lines 28-53, Table III, and Figures 3f and 4b).

Thus, the MCPR-02 antibody does not anticipate Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof inhibits one or more functions associated with binding of a chemokine to said receptor, as MCPR-02 is not disclosed as inhibiting any functions associated with binding of chemokine to CCR2 (e.g., calcium flux or transmigration). In fact, Lind *et al.* teaches the opposite, i.e., that mAb MCPR-02 induces chemotaxis and calcium flux. This distinction is particularly important when considering the use of the claimed antibodies in *in vitro* or *in vivo* applications. For example, administration of the MCPR-02 antibody in clinical situations in which it is desirable to inhibit calcium flux or

chemotaxis of cells expressing CCR2 would be unproductive and possibly detrimental, as the MCPR-02 antibody would not only fail to inhibit the functions associated with binding of chemokine to CCR2, the MCPR-02 antibody could itself induce the undesirable function (e.g., calcium flux or chemotaxis).

Thus, none of the antibodies disclosed by Lind *et al.* anticipate the invention of Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof inhibits binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 5, 6, 8 and 45-57 Under 35 U.S.C. §102(a)

Claims 1, 5, 6, 8 and 45-57 are rejected under 35 U.S.C. §102(a) as being clearly anticipated by Frade *et al.* (*J. Clin. Invest. 100*(3):497-502 (1997); Reference AX; hereinafter "Frade 1"). The Examiner states that Applicant admits on the record that the results taught by said reference could be due to actual antagonistic activity of the antibodies or to receptor desensitization, and that it is apparent that even applicant cannot refute that the antibodies disclosed by the cited reference could be antagonistic. The Examiner concludes that, as a consequence, the antibodies in the cited reference are indeed anticipatory, as they act the same as the antibody Applicant is now claiming. The Examiner further states that since there is no head to head comparison between the prior art products and the Applicant's claimed antibodies, Applicant's assertions are deemed unsupported assertions.

Claims 46-51 have been cancelled. Claims 1, 45 and 52 recite the phrase "wherein said antibody or antigen-binding fragment thereof inhibits binding of a chemokine to said receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor."

Frade 1 discloses the early results of the work which is the basis for the Frade *et al.* reference (*J. Immunology 159*(11):5576-5584 (1997); Reference AW; hereinafter "Frade 2") discussed below. It is clear that Frade 1 pre-dates Frade 2 from two facts. First, Frade 1 was

received for publication on January 28, 1997, while Frade 2 was received for publication on June 13, 1997. Second, Frade 2 cites Frade 1 in its list of references (reference 33).

Frade 1 discloses the production and characterization of several anti-CCR2 antibodies. Some of the antibodies are disclosed as specific for the third extracellular domain (amino acids 273-292). These antibodies plainly do not anticipate Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof binds the amino-terminal domain of CCR2, as this group of antibodies disclosed by Frade 1 bind the third extracellular loop of CCR2.

Frade 1 also discloses antibodies which are described as specific for the amino-terminal domain (amino acids 24-38), and MCP-1R02 is described as being illustrative of this group of antibodies (page 498, col. 2, lines 38-42). Frade 1 states that MCP-1-induced calcium influx and monocyte chemotactic response is blocked by the two CCR2B receptor amino-terminal domain-specific antibodies MCP-1R01 and MCP-1R02 (page 498, col. 2, line 62, through page 499, col. 1, line 8).

The Examiner misinterprets the statement in Applicant's prior Amendment ("However, these results could be due either to actual antagonistic activity of the antibodies or to receptor desensitization due to agonist activity of the antibodies.") as being an admission by Applicant. In fact, this statement was merely a paraphrasing of the explicit statement in Frade 2 that "We also tested for intrinsic mAb activity, as blockage of MCP-1 function in Ca^{2+} influx assays could be due to either antagonist or agonist activity through receptor desensitization." (page 5578, lines 36-38). The nature of the effects of the MCP-1R01 and MCP-1R02 antibodies is clarified in Frade 2, which discloses that upon further study it was determined that stimulation of Fluo-3-loaded Mono Mac 1 cells with MCP-1R02 induces a rapid and transient rise in calcium concentration and transmigration, desensitizing the receptor to MCP-1 (pages 5578, col. 2, line 36, through page 5579, col. 1, line 3). These results make it clear that MCP-1R02 is in fact an agonist which has intrinsic ability to stimulate calcium flux and transmigration (page 5578, line 42 to page 5579, line 3, and Table I of Frade 2). Additionally, Frade 2 discloses that antibody MCP-1R01 has neither agonistic nor antagonistic activity with respect to MCP-1-induced calcium influx and transmigration (Table I of Frade 2).

Thus, an accurate assessment of the teachings of Frade 1 with respect to the functional effects of the anti-CCR2 antibodies disclosed as specific for the amino-terminal domain of CCR2 requires consideration of the teachings of both Frade 1 and Frade 2, as the ordinarily skilled artisan would have been in possession of both references at the time the subject invention was made and would have considered the teachings of Frade 2 in determining what was disclosed in Frade 1. It is clear from the teachings of Frade 2 that the antibodies disclosed in Frade 1 as binding to the amino terminus of CCR2 do not inhibit one or more functions associated with binding of a chemokine to CCR2 (e.g., calcium flux or transmigration). Thus, the antibodies disclosed in Frade 1 do not anticipate the invention of Claims 1, 5, 6, 8, 45 and 52-57, as none of the disclosed antibodies in fact binds the amino terminal domain of CCR2 and inhibits one or more functions associated with binding of a chemokine to CCR2. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 5, 6, 8 and 45-57 Under 35 U.S.C. §102(a)

Claims 1, 5, 6, 8 and 45-57 are rejected under 35 U.S.C. §102(a) as being anticipated by Frade *et al.* (*J. Immunology 159*(11):5576-5584 (1997); Reference AW; hereinafter "Frade 2").

Claims 46-51 have been cancelled. Claims 1, 45 and 52 recite the phrase "wherein said antibody or antigen-binding fragment thereof inhibits binding of a chemokine to said receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor."

Applicant maintains the position that Frade 2 does not anticipate the claimed invention. Frade 2 discloses some of the same subject matter as U.S. Patent No. 6,084,075 to Lind *et al.* (Reference A and AC) discussed above. Specifically, Frade 2 discloses antibodies which bind to CCR2. Some of the antibodies disclosed by Frade 2 (antibodies MCP-1R03, MCP-1R04, MCP-1R05 and MCP-1R06) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the third extracellular loop (amino acids 273-292) of CCR2. In Table I, at page 5578, Frade 2 states that these antibodies recognize amino acids 273-292 of CCR2. These antibodies plainly do not anticipate Claims 1, 5, 6, 8, 45 and 52-57, which recite that the

antibody or antigen-binding fragment thereof binds the amino-terminal domain of CCR2, as these antibodies do not bind the amino terminal domain of CCR2.

The MCP-1R01 and MCP-1R02 antibodies disclosed by Frade 2 were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the amino-terminal domain (amino acids 24-38) of CCR2. In Table I (page 5578), Frade 2 states that these antibodies recognize amino acids 24-38 of CCR2. However, Table I also provides a summary of the activities of MCP-1R01 and MCP-1R02. MCP-1R01 is disclosed as being neither an agonist nor an antagonist of MCP-1-induced calcium influx or transmigration (Table I), i.e., MCP-1R01 neither induced nor inhibited calcium flux and transmigration. Thus, the MCP-1R01 antibody does not anticipate Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof inhibits one or more functions associated with binding of the chemokine to said receptor, as MCP-1R01 is not disclosed as inhibiting any functions associated with binding of chemokine to CCR2 (e.g., calcium flux or transmigration).

MCP-1R02 is disclosed as being an agonist of MCP-1-induced calcium influx and transmigration (Table I). That is, MCP-1R02 is disclosed as stimulating both chemotaxis and calcium influx (page 5578, line 42, to page 5579, line 3, and Figures 3A and 3B), which are functions associated with binding of chemokine to CCR2. Thus, the MCP-1R02 antibody does not anticipate Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof inhibits one or more functions associated with binding of a chemokine to said receptor, as MCP-1R02 is not disclosed as inhibiting any functions associated with binding of chemokine to CCR2 (e.g., calcium flux or transmigration). In fact, Frade 2 teaches the opposite, i.e., that mAb MCP-1R02 induces chemotaxis and calcium flux.

Thus, none of the antibodies disclosed by Frade 2 anticipate the invention of Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof inhibits binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 5, 6, 8 and 45-57 Under 35 U.S.C. §102(a)

Claims 1, 5, 6, 8 and 45-57 are rejected under 35 U.S.C. §102(a) as being anticipated by Lind *et al.* (WO 97/31949; Reference AL).

Claims 46-51 have been cancelled. Claims 1, 45 and 52 recite the phrase "wherein said antibody or antigen-binding fragment thereof inhibits binding of a chemokine to said receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor."

Lind *et al.* discloses antibodies which bind to CCR2. Some of the antibodies disclosed by Lind *et al.* (antibodies MCPR-03, MCPR-04, MCPR-05 and MCPR-06) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the third extracellular loop (amino acids 273-292) of CCR2. In Table III (page 25), Lind *et al.* states that these antibodies recognize amino acids 273-292 of CCR2. These antibodies plainly do not anticipate Claims 1, 5, 6, 8, 45 and 52, as amended, which recite that the antibody or antigen-binding fragment thereof binds the amino-terminal domain of CCR2, as these antibodies do not bind the amino-terminal domain of CCR2.

The rest of the antibodies disclosed by Lind *et al.* (MCPR-01 and MCPR-02) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the amino-terminal domain (amino acids 24-38) of CCR2. However, Table III (page 25) also provides a summary of the activities of MCPR-01 and MCPR-02. MCPR-01 is disclosed as being neither an agonist nor an antagonist of MCP-1-induced calcium influx or transmigration (Table III), i.e., MCPR-01 neither induced nor inhibited calcium flux and transmigration. Thus, the MCPR-01 antibody does not anticipate Claims 1, 5, 6, 8, 45 and 52-57, which recite that the antibody or antigen-binding fragment thereof inhibits one or more functions associated with binding of the chemokine to said receptor, as MCPR-01 is not disclosed as inhibiting any functions associated with binding of chemokine to CCR2 (e.g., calcium flux or transmigration).

MCPR-02, the antibody particularly noted by the Examiner, is disclosed as being an agonist of MCP-1-induced calcium influx and transmigration (Table III). That is, MCPR-02 is disclosed as stimulating both chemotaxis and calcium influx, which are functions associated with binding of chemokine to CCR2. Thus, the MCPR-02 antibody does not anticipate Claims 1, 5, 6,